Title Page

Protocol Title:		A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease	
Protocol Number:		TB006AD2104	
Amendment:		2.0	
Compound:		TB006	
Indication:		Alzheimer's Disease	
Study Phase:		Phase 2	
Short Title:		An open-label long term extension study to assess the safety of TB006 in patients with Alzheimer's Disease	
Acronym:		NA	
Sponsor	**Sponsor Name:**	TrueBinding, Inc.	
	Legal Registered Address:	[redacted]	
Regulatory Agency Identifier Number(s):		**Registry**	**Identifier Number**
		NCT	Not Applicable
Protocol Version and Date:		**Document Version**	**Date**
		Original (v1.0)	21 Jun 2022
		Amendment 1 (v2.0)	26 Jul 2022
		Amendment 2 (v3.0)	16 Feb 2023

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SPONSOR SIGNATORY

Protocol Number: TB006AD2104

Protocol Title:

A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease

I, the undersigned, have approved of the clinical trial protocol amendment with the date of 16 Feb 2023.

Name and Title	Signature and Date
[redacted]	

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR AGREEMENT

Protocol Number: TB006AD2104

Protocol Title:

A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by TrueBinding, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about TB006, understand this study, and are able to comply.

_____ _____

Principal Investigator Name (printed) Signature

_____

Date

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List of Abbreviations

Aβ	amyloid beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0-\tau}$	area under the curve to the end of the dosing period
BMI	body mass index
CDR	Cognitive Drug Research system
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Corona virus disease of 2019
CRF	Case Report Form
CRO	Contract Research Organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	arithmetic coefficients of variation
De novo	Previously untreated patients not enrolled in lead-in Protocol TB006AD2102
DILI	drug-induced liver injury
DRE	disease-related event
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic Case Report Form

EoS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EuroQol	EuroQuality of life
FSH	follicle-stimulating hormone
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
GCV%	geometric coefficients of variation
GLP	Good Laboratory Practice
GSD	geometric standard deviation
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
LAR	legally authorized representative
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
[redacted]	[redacted]
n	number
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NOAEL	no-observed-adverse-effect level

[redacted]	[redacted]
[redacted]	[redacted]
OLE	open-label extension
PD	pharmacodynamic(s)
PDS	pharmacodynamic analysis set
[redacted]	[redacted]
PK	pharmacokinetic
PKS	pharmacokinetic analysis set
PI	Principal Investigator
PK	pharmacokinetic(s)
PKS	PK analysis set
PT	preferred term
Q1	first quartile
q28day	every 28 days
Q3	third quartile
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QW	weekly
SAD	single ascending dose
SAS	safety analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of assessment
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WHO DD	World Health Organization Drug Dictionary
WOCBP	woman of child-bearing potential
WONCBP	woman of non-child-bearing potential

1. Protocol Summary

1.1. Synopsis

Protocol Title:
A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease

Brief Title:
An open-label long term extension study to assess the safety of TB006 in patients with Alzheimer's Disease

Indication:
Alzheimer's Disease

Rationale:
The TB006 nonclinical pharmacology program establishes its potential as a therapeutic agent for Alzheimer's Disease (AD) by neutralizing Galectin-3 (Gal-3), which regulates the production and accumulation of amyloid beta (Aβ and tau proteins and is overexpressed in AD. The preclinical data have shown evidence of addressing underlying disease pathology and improving cognition.

The preclinical safety profile of TB006 further supports the clinical investigation of TB006.

This is an open-label long term extension of the double-blind (TB006AD2102) study in patients who have completed Protocol TB006AD2102 and in eligible de novo patients with AD. This study is designed to evaluate the long-term safety and tolerability of monthly dose infusions of TB006 in patients with AD. In addition, the longitudinal effect of TB006 on cognition, using the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), the Mini Mental State Examination (MMSE, Cognitive Drug Research system (CDR) battery, the Neuropsychiatry Inventory (NPI), the EuroQuality of life (EuroQol) 5-Dimension 5-Level (EQ-5D-5L), [redacted] respectively. In addition to patients from the lead-in protocol, de novo patients will provide additional long-term safety data, considering the expected low study completion rate in this 2-year study.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine the long-term safety and tolerability of monthly doses of TB006	• Safety endpoints, including the incidence of AEs, and, SAEs, as well as assessment of clinical laboratory parameters, vital signs, ECGs, C-SSRS, [redacted] and physical and neurological examinations, until Week 113 after the first TB006 dosing
• To determine the PK profile of monthly doses of TB006	• Plasma concentration of TB006 over time.
• To assess the immunogenicity of TB006 (production of anti-TB006 antibodies)	• Detection of anti-TB006 antibodies
Secondary	
• To determine the effects of monthly TB006 doses on disease progression or recovery using standard measures of cognition and quality of life	• Change from Baseline through Week 101 on the CDR-SB score • Change from Baseline through Week 101 on the CDR battery composite scores and individual task measures • Change from Baseline through Week 101 on the MMSE score • Change from Baseline through Week 101 on the NPI score • Change from Baseline through Week 101 on the EQ-5D 5L QoL total score [redacted]
Exploratory	
• To determine the PD effects of TB006 on plasma AD biomarkers	[redacted]

[redacted]; AD = Alzheimer's Disease; AEs = adverse events; CDR = Cognitive Drug Research System; CDR-SB = Clinical Dementia Rating-Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; [redacted]; MMSE = Mini Mental Status Exam; [redacted] NPI = Neuropsychiatric Inventory; [redacted] PD = pharmacodynamic PK = pharmacokinetic(s); SAE = serious adverse event.

Overall Design:
This is an open-label extension (OLE) study for patients with AD who have 1) completed Protocol TB006AD2102 (lead-in study), or 2) would have been eligible for the lead-in study but were not enrolled (de novo). This OLE study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TB006. The total study duration for each patient will be up to 113 weeks.

Enrollment into this study may begin immediately upon completion of the end of study (EoS) procedures of the lead-in study, with the first dose administered the same day or within 28 days post EoS procedures. For these patients, the EoS procedures conducted in Protocol TB006AD2102 will be used as baseline values for this OLE study. Patients completing the lead-in study more than 28 days prior to the start of the OLE study must undergo screening procedures with the exception of imaging. De novo patients will be identified by the sponsor and referred to one of the participating sites. De novo patients must undergo all screening procedures. Eligibility must be confirmed (de novo patients) or reconfirmed (lead-in study patients).

In this study, all patients will receive TB006 at a dose of 4,000 mg via a 1-hour continuous IV infusion every 28 days (± 5 days). Patients will remain in the clinic for at least 2 hours following the end of the infusion for observation and safety assessments.

Patients will return to the clinic every 28 days for dose administration and safety assessments. All visits have a window of 11 days (± 5 days from scheduled visit). This window is based on the original schedule at the start of the study, planned every 28 days, so if a patient deviates within the window, the original schedule is retained.

Patients will perform a battery of cognition, quality of life tests [redacted], including the MMSE, the CDR-SB, the CDR, the EQ-5D-5L, and the NPI. [redacted] All procedures and study assessments are presented in the Schedule of Assessments table (SoA) (Table 1). Patients will return to the clinic approximately 3 months following the last dose according to Table 1 for the follow-up visit, which includes safety assessments, cognition testing, and PK sampling. If a patient reports any adverse events (AEs), they may be required to return to the clinical unit at the discretion of the investigator for additional assessments. All AEs must be followed to adequate resolution.

Brief Summary:
The purpose of this study is to evaluate the long-term safety and tolerability of TB006 in patients with AD.

Study details include:
- The study duration will be up to 113 weeks.
- The treatment duration will be up to 101 weeks.
- The safety follow-up will be up to 12 weeks.
- The visit frequency will be every 28 days.

Number of Participants:
All eligible patients completing the lead-in study will be offered the opportunity to participate in the current OLE study. Based on historical participation rates, the proposed number of enrolled patients from the lead-in study will be 100 to 120. Additionally, up to 50 de novo patients, identified by the sponsor, may be included. Therefore, a total of approximately 150 to 180 patients will be enrolled.

Intervention Groups:

This is an OLE study, and all enrolled patients will receive TB006.

Summary of Key Eligibility Criteria:
Lead-in study patients are eligible to be included in the study only if all of the following criteria apply:

1. Completed lead-in Protocol TB006AD2102 (patients from both study drug and placebo groups) or are eligible for the lead-in study but were not enrolled (de novo).
    - Completion of Protocol TB006AD2102 is defined as: i) following through to the Day 104 visit or ii) early withdrawal for reasons other than adverse events after receiving at least 1 dose of study drug and completing the early termination visit. Patients who prematurely discontinued for reasons other than adverse events may be considered on a case-by-case basis with the Medical Monitor/Scientific Director of the sponsor.
2. Eligibility must be reconfirmed by the investigator for patients who have a gap of more than 28 days between lead-in Protocol TB006AD2102 completion and enrollment in the current study. These patients will undergo the screening procedures in the current OLE protocol, with the exception of imaging.
3. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    a. Male patients:

    Male patients are eligible to participate if they agree to the following from the first day of dosing through 6 months following the last dose of study drug:
    - Refrain from donating sperm

    PLUS, either:
    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent unless partner is not a woman of child-bearing potential (WOCBP).

    OR
    - Must agree to use contraception/barrier as detailed below:
        - Agree to use a male condom and female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year when having sexual intercourse with a WOCBP who is not currently pregnant.

b. Females must be of non-childbearing potential defined as:
   - At least 12 months post-menopausal.
   - Surgically sterile, resulting from but not limited to tubal ligation, hysterectomy, and oophorectomy.
   - Documented infertility from other causes, such as endometriosis or uterine fibroids.
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. Further details on woman of non-child-bearing potential (WONCBP) are outlined in Appendix 10.4.1.

4. Patients or caregiver has the ability to understand the purpose and risks of the study and provide signed and dated informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol. Patients whose caregiver signs the informed consent must provide their assent.
5. Either currently or previously (in pre-AD condition) literate and capable of reading, writing, and communicating effectively with others.
6. Investigator believes the patient, along with the caregiver, will be compliant with study visits, procedure.

De novo patients, identified by the sponsor and referred to a participating site, are eligible to be included in the study only if all of the following criteria apply:

1. Male and/or female > 50 years of age at the time of signing the informed consent.
2. Body weight of ≥ 50 kg and body mass index (BMI) between 18 and 35 kg/m^2, inclusive.
3. MMSE score of 24 or less.
4. Must be ambulatory.
5. Clinical diagnosis of AD consistent with the following:
   a. Probable AD, according to National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) outlined in Section 10.5.
   b. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) – Criteria for Major Neurocognitive Disorder (previously dementia) outlined in Section 10.7.1.
6. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   a. Male patients:

      Male patients are eligible to participate if they agree to the following from the first day of dosing until at least 90 days after dosing:

      - Refrain from donating sperm.

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent unless partner is not a WOCBP.

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom and female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year when having sexual intercourse with a WOCBP who is not currently pregnant.

b. Females must be of non-childbearing potential defined as:
   - At least 12 months post-menopausal.
   - Surgically sterile, resulting from but not limited to tubal ligation, hysterectomy, and oophorectomy.
   - Documented infertility from other causes, such as endometriosis or uterine fibroids.
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

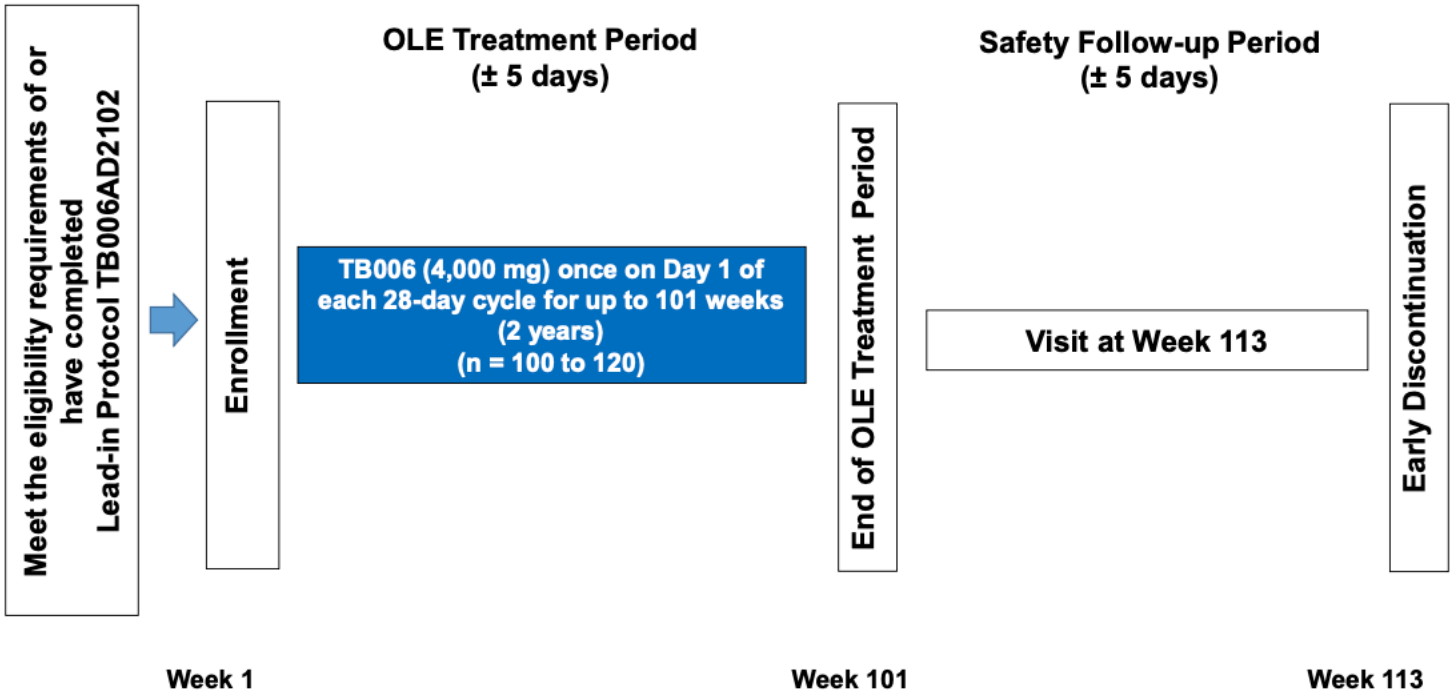
7. Patients or caregiver has the ability to understand the purpose and risks of the study and provide signed and dated informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Patients whose caregiver signs the informed consent must provide their assent.
8. May or may not be receiving 1 or more of the currently marketed cognition enhancing AD medications, including, but not limited to donepezil, memantine, rivastigmine, and galantamine. If receiving, it must be the same medication and dose the past 2 months prior to screening.
9. Either currently or previously (in pre-AD condition) literate and capable of reading, writing, and communicating effectively with others.

Summary of Statistical Considerations:

No formal statistical hypothesis testing will be performed in this study. All demographic, safety, PK, and PD data will be listed and summarized in tabular format by descriptive number [n], mean, standard deviation [SD], median, first and third quartile [Q1, Q3], minimum and maximum) and/or summary (n [%]) statistics as appropriate. PK data will also be displayed graphically as appropriate.

Data Monitoring/Other Committee: No

1.2. Schema



OLE = open-label extension

1.3. Schedule of Activities (SoA)

Table 1. Schedule of Activities

Study Period	SCR	Study Drug Administration Period (all visits ± 5 days)																										
Study Week	(Days -28 or -42 to -1)[a]	1	5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	113 or E/T
General and Safety Assessments																												
Informed consent	X																											
Eligibility criteria	X																											
Demography	X																											
Physical (including height and weight) & neurological examination[b]	X							X							X							X						X
Medical history (includes substance use)	X																											
12-lead ECG[c]	X	X		X		X		X			X			X			X			X							X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																												
Viral serology (HbsAg, IGM anti-HBc, anti-HCV) and COVID-19 testing	X																											
Urine drug and alcohol breathalyzer screening	X	X						X							X							X					X	

Study Period	SCR	Study Drug Administration Period (all visits ± 5 days)																										
Study Week	(Days -28 or -42 to -1)[a]	1	5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	113 or E/T
Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)	X				X			X							X							X						X
Efficacy and Pharmacodynamic Assessments: Cognition Testing, [redacted] and Blood Samples																												
[redacted]	[redacted]							[redacted]						[redacted]														[redacted]
[redacted]	[redacted]							[redacted]						[redacted]														[redacted]
Cognition/QoL testing[h]	X				X			X							X				X				X				X	X
[redacted]	[redacted]				[redacted]			[redacted]						[redacted]						[redacted]							[redacted]		[redacted]
Study Treatment																												
Study drug IV infusion[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics and Immunogenicity Assessments																												
Blood sample for PK assessment[k]	X	X	X	X	X	X	X	X					X							X							X	X
ADA assessment		X						X					X							X								X

ADA = anti-drug antibody; AE = adverse event; anti-HBc = hepatitis B core antibodies; anti-HCV = hepatitis C virus antibodies; COVID-19 = coronavirus disease of 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L and/or QoL = EuroQuality of life 5-Dimension 5-Level and/or quality of life assessment; E/T = early termination visit; HbsAg = hepatitis B surface antigen; IGM = immunoglobulin M antibodies; IV = intravenous(ly); [redacted] PD = pharmacodynamic; [redacted] PK = pharmacokinetic; q28day = every 28 days; SCR = screening.

a For patients dosed within 28 days of their EoS procedures from lead-in Protocol TB006AD2102, the EoS procedures will be used as baseline for this study. For de novo patients and patients dosed > 28 days from EoS procedures in lead-in Protocol TB006AD2102, eligibility must be confirmed or reconfirmed, and screening procedures must be completed per this current OLE protocol, with the exception of imaging (lead-in patients only). Additionally, a 42-day screening period is required for de novo patients.

b Physical examinations at the clinic visits other than the Screening Period and EoS procedures may be brief, focused on abnormalities identified on the Screening examination and as related to adverse events. Physical examination as part of EoS procedures in Protocol TB006AD2102 will be used as baseline assessment for this study if they are done within 28 days.

c Singlets; predose and 2 hours (± 30 minutes) post infusion.

d Predose, then at any time between end of infusion and 2 hours (± 30 minutes) post infusion on dose administration days. Includes oral temperature, heart rate, respiratory rate, blood pressure, and orthostatic blood pressure.
e Collected within ± 2 weeks of the scheduled week.
f [redacted]
[redacted] Section 8.2.3.
h Order of testing: CDR-SB, CDR battery, MMSE, NPI, and (EQ-5D-5L = EuroQol 5-Dimension 5-Level scale).
i [redacted]
j Doses administered q28day on the first day of the week (eg, Days 1, 29, 57, 85, etc.) ± 5 days of the scheduled dosing day.
k All PK samples are predose.

2. Introduction

TB006 is a humanized IgG4 (S228P) type monoclonal antibody, being developed by TrueBinding, Inc. for the treatment of Alzheimer's disease (AD).

2.1. Study Rationale

The TB006 nonclinical pharmacology program establishes its potential as a therapeutic agent for AD by neutralizing Gal-3, which regulates the production and accumulation of Aβ and tau proteins and is overexpressed in AD. The preclinical data have shown evidence of addressing underlying disease pathology and improving cognition.

The preclinical safety profile of TB006 further supports the clinical investigation of TB006.

This is an open-label long term extension of the double-blind (TB006AD2102) study in patients who have completed Protocol TB006AD2102 and in eligible de novo patients with AD. This study is designed to evaluate the long-term safety and tolerability of monthly dose infusions of TB006 in patients with AD. In addition, the longitudinal effect of TB006 on cognition, using the CDR-SB, the MMSE, CDR battery, the NPI, the EQ-5D-5L, as well [redacted] will be evaluated. [redacted] In addition to patients from the lead-in protocol, de novo patients will provide additional long-term safety data, considering the expected low study completion rate in this 2-year study.

2.2. Background

2.2.1. Disease Background

AD is a chronic progressive neurodegenerative disorder and is the leading cause of dementia among older adults. In the US, AD is 1 of the leading causes of death, ranking sixth among US adults and fifth among adults aged 65 years or older (CDC, 2020).

The most common and thoroughly investigated hypotheses proposed to explain the pathophysiology of AD are the amyloid hypothesis and tau hypothesis. Considerable evidence suggests that toxic changes in Aβ and tau initiate the disease cascade. Abnormal tau accumulates to form neurofibrillary tangles inside nerve bodies, where they destroy cell structure and interfere with neuronal function and communication. Eventually, cell death and brain atrophy result.

Other factors that may also contribute to AD include insufficient blood and nutrient delivery of the vascular system to the brain and neuroinflammation which damages neurons in the brain.

Drug development in the dementia arena has been highly active in the past 20 years. There are approximately 5 compounds with market approval, all of which aim to improve the symptoms of

dementia. These ‘symptomatic” treatments may improve cognition in the short term but have no effect on the progression of the disease. More recently, therapies with large molecule antibodies have explored the impact of targeting the underlying pathology such as amyloid or damaged tau.

These treatments seek to modify the course of the disease by slowing disease progression. Although some of these compounds have shown efficacy in patient subtypes and have demonstrated an acceptable safety and tolerability profile in clinical studies (Panza et al, 2019; Van Dyck, 2017), none have met their primary endpoint; ergo none have been approved for marketing. Therefore, an urgent unmet medical need remains for the treatment of AD.

Key to the success of drug development in this patient population is the need to identify patients early in the course of their disease for treatment intervention. Patients with advanced symptomatic disease have significant demyelination, neuronal cell loss, and loss of volume. [redacted] NIA, 2020 Risacher and Saykin, 2013

2.2.2. TrueBinding, Inc. Investigational Product Background: TB006

Galectins are a ubiquitous group of proteins found in a variety of cells and tissues and are involved in numerous metabolic processes and functions. At least 15 galectin isotypes have been identified in epithelial cells of the respiratory system, digestive tract, urinary tract, skin, cardiovascular system, liver, immune cells, and in the CNS. Gal-3 plays an important role in different pathogenic conditions, including in neuroinflammatory and neurodegenerative disorders such as multiple sclerosis, AD, Parkinson’s disease, and Huntington’s disease. In addition, Gal-3 also plays a protective role due to its anti-apoptotic effect in target cells. In vivo data from several investigators suggest that Gal-3 may be an important therapeutic target in pathological conditions including the disorders of the CNS.

TB006 is a humanized IgG4 (S228P) type monoclonal antibody that is highly specific and has high affinity to human Gal-3. It has demonstrated the potential to treat neurodegenerative disorders such as AD and traumatic brain injury, with an apparent wide safety margin, in preclinical models.

A detailed description of the chemistry, pharmacology, efficacy, and safety of TB006 is provided in the IB.

2.3. Benefit/Risk Assessment

Based on preclinical pharmacology data, nonclinical toxicity studies, and the safety and tolerability demonstrated in clinical studies to date, the overall benefit/risk profile favors clinical development of TB006 for treatment of AD.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of TB006 may be found in the IB.

2.3.1. Risk Assessment

A standard battery of toxicology studies was conducted with TB006. A pivotal safety 1-month GLP toxicology study was previously conducted to support the SAD study (Protocol TB006HV1101) and combined Phase 1b/2a study in patients with AD (Protocol TB006AD2102) in cynomolgus monkeys. A pivotal 6-month GLP study in cynomolgus monkeys using doses of 3 mg/kg, 30 mg/kg, and 150 mg/kg was recently conducted to support chronic dosing of TB006. This study included a 12-week recovery period and full histology. No treatment related adverse findings, either clinical, laboratory, or histopathology were observed. No other findings were observed in this or any of the other toxicology studies. These data suggest chronic administration of TB006 may be safely studied.

TB006 is a first in class monoclonal antibody, therefore, there are no known class adverse effects or risks to report from clinical studies. In general, risks associated with other monoclonal antibodies include allergic reactions such as hives or itching, flu like symptoms such as chills, fatigue, fever, and muscle aches and pains, nausea and vomiting, skin rashes and decreases in blood pressure. These effects have not been observed in either preclinical or clinical studies to date. Other marketed IgG4 humanized monoclonal antibodies, such as natalizumab, eculizumab, and pembrolizumab, are used clinically. These antibodies largely target the immune system. There appears to be a spectrum of target-related negative effects when the total antibody dose gets too high. This pattern is not evident with TB006 in studies to date but will be closely observed in this study.

When performed correctly and according to industry standards, venipuncture complications are rare. However, even when properly performed, complications can include fainting, dizziness, hematoma, nerve injury, and arterial puncture or laceration. Blood draws and administration of the IV infusion in this study will be performed by adequately trained medical staff to minimize any risk to patients.

The safety assessments to be performed in this study, including clinical chemistry, hematology and urinalysis analyses, vital signs, ECGs, physical and neurological examinations, and assessments of AEs, SAEs, and C-SSRS are standard evaluations to ensure patient safety in this clinical study.

2.3.2. Benefit Assessment

TB006 is a humanized IgG4 (S228P) type monoclonal antibody that is highly specific and has high affinity to human Gal-3. It has demonstrated efficacy in preclinical models of neurodegenerative disorders such as AD and traumatic brain injury, and results are consistent with or superior to other compounds that have advanced into late-stage clinical studies. Thus, there is potential for TB006 to be effective in these disorders. The preclinical safety profile of TB006 and the safety profile in clinical studies to date support the further investigation of TB006 in clinical studies.

Understanding that this therapy may have no clinical benefits to patients themselves, patients in this study will contribute to the process of developing new therapies in an area of unmet need.

Patients will undergo clinical evaluations/assessments associated with study procedures (eg, safety laboratory tests, vital sign and ECG measurements, and physical and neurological examinations), which would be a potential benefit for their own health awareness.

Patient expenses for time, travel, and other costs will be offset by a monetary compensation, consistent with standards for such study participations and after approval from the IRB to ensure that no coercion or undue influence are imposed on patients.

2.3.3. Overall Benefit Risk Conclusion

The above benefit risk assessment supports the conduct of this clinical study.

The preclinical and available clinical data on TB006 to date suggest a wide margin of safety and minimal risk of adverse effects. The risks associated with study procedures, including minimally invasive procedures such as blood draws, are also very low. Any potential adverse effects associated with the study drug and procedures are further minimized by intense safety monitoring and medical oversight by the investigator and study staff. Therefore, the potential risks identified in association with TB006 are justified by the anticipated benefits that may be afforded to patients with AD if TB006 is successfully developed. Single doses as high as 5,000 mg in healthy volunteers and weekly doses as high as 1,000 mg in patients with AD have been administered. While both of these studies are currently blinded, TB006 appears to be safe and well tolerated. The safety findings to date consist of predominantly mild, sporadic, and self-limiting adverse events, one patient who withdrew due to AEs, and 1 unrelated severe SAE.

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with TB006 are justified by the anticipated benefits that may be afforded to patients with AD.

3. Objectives, Endpoints, and Estimands

Table 2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the long-term safety and tolerability of monthly doses of TB006	• Safety endpoints, including the incidence of AEs, and, SAEs, as well as assessment of clinical laboratory parameters, vital signs, ECGs, C-SSRS, [redacted] and physical and neurological examinations, until Week 113 after the first TB006 dosing
• To determine the PK profile of monthly doses of TB006	• Plasma concentration of TB006 over time.
• To assess the immunogenicity of TB006 (production of anti-TB006 antibodies)	• Detection of anti-TB006 antibodies
Secondary	
• To determine the effects of monthly TB006 doses on disease progression or recovery using standard measures of cognition and quality of life	• Change from Baseline through Week 101 on the CDR-SB score • Change from Baseline through Week 101 on the CDR battery composite scores and individual task measures • Change from Baseline through Week 101 on the MMSE score • Change from Baseline through Week 101 on the NPI score • Change from Baseline through Week 101 on the EQ-5D 5L QoL total score [redacted]
Exploratory	
[redacted]	[redacted]

Aβ40 = amyloid beta 40; AD = Alzheimer's Disease; AEs = adverse events; CDR = Cognitive Drug Research System; CDR-SB = Clinical Dementia Rating-Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; Gal-3 = Galactin-3; MMSE = Mini Mental Status Exam; [redacted] NFL = neurofilament light chain; NFH = neurofilament heavy chain; NPI = Neuropsychiatric Inventory; [redacted] PD = pharmacodynamic PK = pharmacokinetic(s); SAE = serious adverse event.

4. Study Design

4.1. Overall Design

This is an open-label extension (OLE) study for patients with AD who 1) have completed Protocol TB006AD2102 (lead-in study) or 2) would have been eligible for the lead-in study but were not enrolled (de novo). This OLE study is designed to evaluate the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of TB006. The total study duration for each patient will be up to 113 weeks.

Enrollment into this study may begin immediately upon completion of the end of study (EoS) procedures of the lead-in study, with the first dose administered the same day or within 28 days post EoS procedures. For these patients, the EoS procedures conducted in Protocol TB006AD2102 will be used as baseline values for this OLE study. Patients completing the lead-in study more than 28 days prior to the start of the OLE study must undergo screening procedures with the exception of imaging. De novo patients will be identified by the sponsor and referred to one of the participating sites. De novo patients must undergo all screening procedures. Eligibility must be confirmed (de novo patients) or reconfirmed (lead-in study patients).

In this study, all patients will receive TB006 at a dose of 4,000 mg via a 1-hour continuous IV infusion q28day (± 5 days). Patients will remain in the clinic for at least 2 hours following the end of the infusion for observation and safety assessments.

Patients will return to the clinic q28day for dose administration and safety assessments. All visits have a window of 11 days (± 5 days from scheduled visit). The window is based on an original visit schedule planned from the start of the study. If a patient deviates within the window, the original schedule is retained. If a patient misses a visit or is outside the window, the visit is typically skipped but the monitor must be notified for further instructions.

Patients will perform a battery of cognition and quality of life tests, [redacted], including the MMSE, the CDR-SB, the CDR, the EQ-5D-5L, and the NPI. [redacted]. All procedures and study assessments are presented in the SoA (Table 1). Patients will return to the clinic approximately 3 months following the last dose according to Table 1 for the follow-up visit, which includes safety assessments, cognition testing, QoL, [redacted], PD, and PK sampling. [redacted] Section 8.2.3. If a patient reports any AEs, they may be required to return to the clinical unit at the discretion of the investigator for additional assessments. All adverse events must be followed to adequate resolution.

4.1.1. Study Duration for an Individual Participant

The duration of the study for each patient is up to 113 weeks. This includes 101 weeks (2 years) of dosing and a 12-week safety follow-up period.

4.1.2. Number of Participants

All eligible patients completing the lead-in study will be offered the opportunity to participate in the current OLE study. Based on historical participation rates, the proposed number of enrolled patients from the lead-in study will be 100 to 120. Additionally, up to 50 de novo patients, identified by the sponsor, may be included. Therefore, a total of approximately 150 to 180 patients will be enrolled.

The sample size determination is present in Section 9.6.

4.1.2.1. Replacement of Participants

Not applicable.

4.1.3. Number of Sites

The same sites participating in the lead-in study will be eligible to participate in the extension study as long as they randomized at least 1 patient. This represents approximately 15 sites in this multi-center study, all in the US.

4.2. Scientific Rationale for Study Design

This is an open-label long-term safety extension of the double-blind study (TB006AD2102) in patients with AD.

An AD patient population is included in this study to determine the safety and tolerability of TB006 in the patient population that is being pursued for development. A mild to severe patient population is the tentative population of interest due to the great medical unmet need and the large opportunity for clinical improvement. TB006 may do more than simply halt disease progression. If it can improve cognition, the mild to severe population is where it is most likely to be detected. Patients who have completed lead-in protocol TB006AD2102 (and have been deemed eligible by the investigator), may participate in this open-label study. In addition to patients from the lead-in protocol, de novo patients will provide additional long-term safety data.

This open-label study is designed to evaluate the long-term safety and tolerability of TB006 in patients with AD. Any approved medication or nonmedical intervention to treat AD are allowed prior to and during this study. Although uncontrolled, the longitudinal effect of TB006 on [redacted] cognition, using the CDR-SB, the MMSE, the CDR battery, and the NPI, the EQ-5D-5L will be evaluated. [redacted] All PD measures will be assessed from baseline in the OLE study.

All safety and efficacy assessments included in this study are standard measures used in clinical studies in general and AD studies in particular.

4.3. Justification for Dose

A SAD study (Protocol TB006HV1101) established the safety, tolerability, and PK of TB006 doses ranging from 70 to 5,000 mg in healthy volunteers. In the ongoing Phase 2 study in patients with AD, escalating doses up to 1,000 mg QW × 5 doses (maximum total dose of 5,000 mg) were also safe and well tolerated). In both studies, exposures C_{max} and AUC) at the highest dose afforded an 8- and 6-fold safety margin, respectively, from the exposures observed in the definitive GLP 1-month toxicology study.

The preclinical safety of TB006 chronic dosing was explored in a 6-month GLP toxicology study in cynomolgus monkeys. The doses used in this study were 3, 30, and 150 mg/kg, administered every two weeks for 6 months. This study included a 12-week recovery period and full histology. Dosing throughout the study was well tolerated. There were no adverse findings of any type, either during the in-life phase or upon histology. Therefore, the NOAEL in cynomolgus monkeys dosed once biweekly for 6 months was 150 mg/kg. The mean steady state exposures associated with this dose across both males and females were C_{max} of approximately 13,500 µg/mL and the ($AUC_{0-\tau}$) of approximately 1,990,000 h*µg/mL. Tau in the study was 2 weeks; when converted to 4 weeks as will be done in this study, the $AUC_{0-\tau}$ is approximately 3,980,600 h*µg/mL.

The preclinical efficacy program established the potential of TB006 in several models of acute neurological and chronic neurodegenerative disorders. Although plasma therapeutic concentration ranges have not been established, the data indicate a positive dose-response relationship across these models. Therefore, the highest projected safe dose tested in the Phase 1 program will likely afford the greatest probability of success. For these reasons, a dose regimen of up to 4,000 mg q28day is selected as the dose level for this study.

The mean steady-state C_{max} and $AUC_{0-\tau}$ from a dose of 4,000 mg q28day are projected from non-parametric super positioning concentrations. The regimens were simulated up to 10,080 hours and took 9,408 to 10,080 hours for a multi-compartment model. These values are 2,640 µg/mL and 1,138,500 h*µg/mL, respectively. These values afford a 5-fold margin from the NOAEL on C_{max} and a 3.5-fold margin on $AUC_{0-\tau}$ at the planned dose of 4,000 mg q28day, adequate margins given the absence of any safety signals in the clinical studies to date.

4.4. End of Study Definition

End of Study (Individual Patient): A patient is considered to have completed the study if the patient has completed all study visits through the Week 113 assessments as shown in the SoA (Table 1).

End of Study (End of Trial): The EoS is defined as the date of the last visit of the last patient in the study or the last scheduled procedure shown in the SoA (Table 1) for the last patient in the study.

5. Study Population

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 10.1.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Lead-in study patients are eligible to be included in the study only if all of the following criteria apply:

1. Completed lead-in Protocol TB006AD2102 (patients from both study drug and placebo groups) or are eligible for the lead-in study but were not enrolled (de novo).
    - Completion of Protocol TB006AD2102 is defined as: i) following through to the Day 104 visit or ii) early withdrawal for reasons other than adverse events after receiving at least 1 dose of study drug and completing the early termination visit. Patients who prematurely discontinued for reasons other than adverse events may be considered on a case-by-case basis with the Medical Monitor/Scientific Director of the sponsor.
2. Eligibility must be reconfirmed by the investigator for patients who have a gap of more than 28 days between lead-in Protocol TB006AD2102 completion and enrollment in the current study. These patients will undergo the screening procedures in the current OLE protocol, with the exception of imaging.
3. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    a. Male patients:

    Male patients are eligible to participate if they agree to the following from the first day of dosing through 6 months following the last dose of study drug:
    - Refrain from donating sperm

    PLUS, either:
    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent unless partner is not a woman of child-bearing potential (WOCBP).

    OR
    - Must agree to use contraception/barrier as detailed below:
        - Agree to use a male condom and female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year when having sexual intercourse with a WOCBP who is not currently pregnant.

    b. Females must be of non-childbearing potential defined as:
    - At least 12 months post-menopausal.

- Surgically sterile, resulting from but not limited to tubal ligation, hysterectomy, and oophorectomy.
- Documented infertility from other causes, such as endometriosis or uterine fibroids.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. Further details on WONCBP are outlined in Appendix 10.4.1.

4. Patients or caregiver has the ability to understand the purpose and risks of the study and provide signed and dated informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol. Patients whose caregiver signs the informed consent must provide their assent.
5. Either currently or previously (in pre-AD condition) literate and capable of reading, writing, and communicating effectively with others.
6. Investigator believes the patient, along with the caregiver, will be compliant with study visits, procedure.

De novo patients, identified by the sponsor and referred to a participating site, are eligible to be included in the study only if all of the following criteria apply:

1. Male and/or female > 50 years of age at the time of signing the informed consent.
2. Body weight of ≥ 50 kg and BMI between 18 and 35 kg/m^2, inclusive.
3. MMSE score of 24 or less.
4. Must be ambulatory.
5. Clinical diagnosis of AD consistent with the following:
   a. Probable AD, according to NINCDS-ADRDA outlined in Section 10.5.
   b. Meets the DSM-5 – Criteria for Major Neurocognitive Disorder (previously dementia) outlined in Section 10.7.1.
6. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   a. Male patients:

      Male patients are eligible to participate if they agree to the following from the first day of dosing until at least 90 days after dosing:

      - Refrain from donating sperm.

        PLUS, either:

      - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent unless partner is not a WOCBP.

        OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom and female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year when having sexual intercourse with a WOCBP who is not currently pregnant.

b. Females must be of non-childbearing potential defined as:
- At least 12 months post-menopausal.
- Surgically sterile, resulting from but not limited to tubal ligation, hysterectomy, and oophorectomy.
- Documented infertility from other causes, such as endometriosis or uterine fibroids.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

7. Patients or caregiver has the ability to understand the purpose and risks of the study and provide signed and dated informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Patients whose caregiver signs the informed consent must provide their assent.
8. May or may not be receiving 1 or more of the currently marketed cognition enhancing AD medications, including, but not limited to donepezil, memantine, rivastigmine, and galantamine. If receiving, it must be the same medication and dose the past 2 months prior to screening.
9. Either currently or previously (in pre-AD condition) literate and capable of reading, writing, and communicating effectively with others.

5.2. Exclusion Criteria

Lead-in study patients are excluded from the study if any of the following criteria apply:

1. Development of an intolerable adverse event or an adverse event that was considered an important safety risk in Protocol TB006AD2102.
2. Any of the following emerging medical or psychiatric exclusion criteria as defined in the lead-in Protocol TB006AD2102.
   a. Any medical or neurological condition other than AD that in the opinion of the investigator could be a contributing cause of the patient's dementia (eg, medication use, vitamin B12 deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, diffuse Lewy body disease, or head trauma).
   b. History within the past 6 months or evidence of clinically significant psychiatric illness (eg, major depression, schizophrenia, or bipolar affective disorder).

c. Diagnosis of a dementia-related CNS disease other than AD (eg, Parkinson's Disease, Huntington's Disease, frontotemporal dementia, multi-infarct dementia, dementia with Lewy bodies, or normal pressure hydrocephalus).

[redacted]

e. [redacted]

f. Any untreated or unstable clinically significant medical condition (ie, hypertension, diabetes, chronic obstructive pulmonary disorder, asthma, or depression, etc.) in the opinion of the investigator.

g. Any clinically significant findings in medical examination, including physical examination, 12-lead ECG, clinical laboratory tests (specifically, ALT > 1.5 × ULN, bilirubin > 1.5 × ULN [bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%], QTcB > 520 msec).

h. Undergone major surgery ≤ 2 months before study drug administration.

i. Loss of more than 100 mL blood (eg, a blood donation) within 2 months before first study drug administration, or has received any blood, plasma, or platelet transfusions within 3 months before Day 1, or plans to donate blood during the study or within 3 months after the study.

j. Regular alcohol consumption within 6 months prior to the study defined as: an average QW intake of > 20 units for males or > 16 units for females. One unit is equivalent to 8 grams of alcohol: a half pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.

k. Meets DSM-5 criteria for moderate or severe substance use disorder within the past 12 months, or has a positive test for substances of abuse, or has used substances, including but not limited to opiates, methadone, buprenorphine, methamphetamine, cocaine, amphetamines recreationally within the past 12 months.

l. Unable to complete this study for other reasons or the investigator believes the patient should be excluded.

3. Since participating in Protocol TB006AD2102, the patient has participated in another drug, biologic, device, or a clinical study or treatment with an investigational drug or approved therapy for investigational use.
4. Any clinically significant findings in medical examination. This includes physical examination, 12-lead ECG, or clinical laboratory tests on the final visit in Protocol TB006AD2102 or on the Baseline visit in this study. Patients who are Covid-19-positive at Screening (or EOT from lead-in study) must delay the start of the study until they are Covid-19-negative. They may be retested at weekly intervals.

5. Patients who have undergone major surgery since enrollment in Protocol TB006AD2102 will be considered on a case-by-basis.

De novo patients are excluded from the study if any of the following criteria apply:

1. Any medical or neurological condition other than AD that in the opinion of the investigator could be a contributing cause of the patient's dementia (eg, medication use, vitamin B12 deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, diffuse Lewy body disease, head trauma).
2. History within the past 6 months or evidence of clinically significant psychiatric illness (eg, major depression, schizophrenia, or bipolar affective disorder).
3. Diagnosis of a dementia-related CNS disease other than AD (eg, Parkinson's Disease, Huntington's Disease, frontotemporal dementia, multi-infarct dementia, dementia with Lewy bodies, normal pressure hydrocephalus).

[redacted]

5. Participation in any other drug, biologic, device, or clinical study or treatment with any investigational drug or approved therapy for investigational use within 30 days (or 5 half-lives, whichever is longer) prior to screening, and/or participation in any other clinical study involving experimental medications for AD within the 60 days (or 5 half-lives, whichever is longer) prior to screening.

[redacted]

7. Any untreated or unstable clinically significant medical condition (ie, hypertension, diabetes, chronic obstructive pulmonary disorder, asthma, depression, etc.) as judged by the investigator.
8. Any clinically significant findings in medical examination, including physical examination, 12-lead ECG, clinical laboratory tests (specifically, ALT > 1.5 × ULN, bilirubin > 1.5 × ULN [bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%], QTcB > 450 msec for male patients or > 470 msec for female patients).
9. Undergone major surgery ≤ 2 months before study drug administration.
10. Loss of more than 100 mL blood (eg, a blood donation) within 2 months before first study drug administration, or has received any blood, plasma, or platelet transfusions within 3 months before Day 1, or plans to donate blood during the study or within 3 months after the study.
11. Recent (3-month) history of a positive COVID-19 test result or disease symptoms of COVID-19 disease such as shortness of breath, cough, rhinorrhea, and sore throat, etc.
12. Known history of, or a positive test result for, HBsAg, IgM anti HBc, anti HCV, or HIV types 1 or 2 at screening. Patients with a documented history of treatment for Hepatitis C are otherwise eligible to participate.

13. Regular alcohol consumption within 6 months prior to the study defined as: an average qw intake of > 20 units for males or > 16 units for females. One unit is equivalent to 8 grams of alcohol: a half pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
14. Meets DSM-5 criteria for moderate or severe substance use disorder within the past 12 months, or has a positive test for substances of abuse, or has used substances, including but not limited to opiates, methadone, buprenorphine, methamphetamine, cocaine, amphetamines recreationally within the past 12 months.
15. Unable to complete this study for other reasons or the investigator believes that he or she should be excluded.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No fasting or other dietary restrictions, including caffeine, are applicable. Dietary restrictions may apply to patients undergoing [redacted] These restrictions could include reduced carbohydrate intake for up to 24 hours and fasting for 6 hours prior to the procedure.

5.3.2. Alcohol

Moderate alcohol consumption (up to 2 units/day [males] and 1 unit/day [females]) is allowed throughout the study. One unit is equivalent to 8 grams of alcohol: a half pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.

5.3.3. Activity

Patients will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Patients may participate in light recreational activities during the study (eg, moderate exercise such as walking or bicycling).

5.4. Screen Failures

A screen failure occurs when a patient who consents to participate in the clinical study does not participate in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if they have the potential to be included. Patients who have completed lead-in Protocol TB006AD2102 and experience a gap of more than 28 days between completion of lead-in and enrollment in OLE study, eligibility must be screened for reconfirmation. De novo

patients must undergo all screening procedures. Rescreened patients should be assigned the same patient number as for the initial screening. Informed consent is required before patients can be rescreened. See Section 10.1.3 for Informed Consent Process details.

5.5. Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), intended to be administered to a study patient according to the study protocol.

Refer to the Study Reference Manual/Pharmacy Manual/IB for more detailed information regarding the storage, preparation, destruction, and administration of treatment.

A concomitant therapy is any medication or treatment the patient received between enrollment in this OLE study (de novo patients) or the lead-in Protocol TB006AD2102, through Week 113 of this study, or early discontinuation (whichever is early).

6.1. Study Intervention(s) Administered

The study drug is TB006, a humanized monoclonal antibody which binds to gal-3. TB006 will be administered as a 1-hour IV infusion at 4,000 mg TB006 with the use of a 0.2-micron filter as outlined in Table 3. Patients will be observed in the clinic for at least 2 hours following the end of the infusion for observation and safety assessments.

Table 3. Study Intervention(s) Administered

Drug Name	Treatment	Placebo
Intervention Name	TB006	Not applicable.
Intervention Description	IV administration of 4,000 mg q28day	
Type	Drug	
Dose Formulation	Clear to slightly opalescent, sterile solution for injection	
Unit Dose Strength(s)	20 mg/mL in 8 mL vial (160 mg total)	
Dosage Level(s)	Prior to administration, the correct dosage of TB006 will be added to 300 mL of sterile normal saline for injection, USP, for a total of 500 mL, then infused over 1-hour q28day ± 5 days. Drug preparation and administration instructions will be provided in a separate Pharmacy Manual	
Route of Administration	IV infusion over 1 hour with the use of a 0.2-micron filter.	
Use	Experimental	
Sourcing	Provided centrally by the Sponsor	
Packaging and Labeling	TB006 will be provided as single-use sterile injectable glass vials sealed with rubber stoppers and aluminum plain flip tops. Each vial will be labeled as required per country requirement. TB006 should always be stored at 2ºC to 8ºC (36ºF to 46ºF).	

IV = intravenous(ly); q28day = every 28 days; USP = United States Pharmacopeia

6.2. Preparation, Handling, Storage, and Accountability

TB006 sterilized liquid drug product is supplied in 8 mL glass vials, sealed with a rubber stopper and an aluminum flip top, containing 160 mg (20 mg/mL) TB006 drug product per vial. TB006 drug product should always be stored at 2ºC to 8ºC (36ºF to 46ºF).

- TB006 drug product should be administered via IV infusion over 60 minutes, after adding the proper volume (200 mL) to an IV bag containing 300 mL of 0.9% Sodium Chloride Injection, USP (normal saline) for a total of 500 mL. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only patients enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or other specified location.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; all patients will be treated with TB006 and there is no randomization or blinding.

6.4. Study Intervention Compliance

When the individual dose for a patient is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When patients are dosed at the site, they will receive the study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the quantity of TB006 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded.

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

There will be no post-study access to the study drug for any of the patients.

6.7. Treatment of Overdose

For this study, any dose of study drug greater than the planned doses of study drug indicated in this protocol, will be considered an overdose. There is no recommendation for a specific treatment for an overdose.

- Contact the Medical/Scientific Monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until TB006 can no longer be detected systemically until the next scheduled dose.
- Obtain a plasma sample for PK analysis according to the protocol schedule unless otherwise advised by the Medical/Scientific Monitor.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical/Scientific Monitor based on the clinical evaluation of the patient.

6.8. Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) the patient was receiving at the time of enrollment in this OLE study or in lead-in Protocol TB006AD2102, or receives during this study must be recorded along with:

- Reason for use.
- Dates of administration, including start and end dates.
- Dosage information, including dose and frequency.

The Medical/Scientific monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Any approved medication or nonmedical intervention to treat AD are allowed prior to and during this study.

Other medications to treat stable, chronic medical conditions are acceptable. For de novo patients, these must have been started more than 30 days before screening. Patients who have experienced a gap of greater than 28 days between completion of the lead-in protocol and the

OLE study, and de novo patients, who have been placed on medications for an acute (ie, < 2 weeks) situation, such as infection or pain, should complete the course of treatment before beginning enrollment in the current study. In general, the use of other monoclonal antibodies on a chronic basis must be approved by the Medical/Scientific Monitor:

Paracetamol/acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study.

Any questions or uncertainties about concomitant medication may be discussed with the Medical/Scientific Monitor.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Patients have the right to withdraw from investigational product and/or other protocol required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a patient(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety, efficacy, immunogenicity, and PK, for 3 additional months. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up, and for any further evaluations that need to be completed.

Reasons for removal from study drug and/or from the study include any of the following:

- Liver injury (see following Section 7.1.1)
- Cardiac changes (see following Section 7.1.2)
- Adverse events
- Significant protocol deviation
- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that poses a greater risk to the patient with continued participation
- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well being
- Sponsor decision
- Patient request to discontinue study drug or withdraw consent for study participation
- Death
- Lost to follow-up

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets 1 of the conditions outlined Section 10.6 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2. QTc Stopping Criteria

A patient who meets the below criteria based on ECG readings will be withdrawn from the study:

- Change from Baseline: sustained QTc > 60 msec

  If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcB or QTcF after study drug infusion), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. The latter is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1). If possible, a safety follow-up visit should be conducted 3 months later. See SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls, and if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

  Discontinuation of specific sites or of the study as a whole are handled in Section 10.1.10.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed. Specifications related to protocol deviations are presented in Section 10.1.9.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).
- The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 166 mL (Table 4).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. General Assessments

8.1.1. Screening, Enrollment, and Baseline

Patients who have completed lead-in Protocol TB006AD2102 (either Part 1 or Part 2) and up to 50 de novo patients are eligible to participate in this OLE study. There is no formal screening period for patients enrolled from the lead-in study. The final visit (Day 104) from the lead-in study will be used as the baseline assessment for the current study. De novo patients and patients from the lead-in study with a gap of more than 28 days between the lead-in study and this study, must undergo screening procedures as outlined in the SoA (Table 1).

Informed consent will be obtained after the study has been fully explained to the patient and before the conduct of any assessments (Section 10.1.3) for the informed consent procedure).

8.1.2. Demographics and Medical History

Demographics and medical history collected in the TB006AD2102 (lead-in) study will be reviewed at the end of the TB006AD2102 study/Baseline Visit 1 (first visit of the OLE study).

Demographics and medical history for de novo patients will be collected and reviewed prior to enrollment in the current study.

8.1.3. Prior Therapy

Prior therapies including currently marketed cognition enhancing AD medication being taken or received during lead-in Protocol TB006AD2102 will be reviewed at the end of that study, and during the first baseline visit of this OLE study (lead-in and de novo patients).

8.1.4. Safety follow up

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.2. Efficacy Assessments

The efficacy assessment scale(s) selected for this study are the list of scales for the efficacy endpoints. Planned timepoints for all efficacy assessments are provided in the SoA (Table 1). Every effort should be made to ensure that the protocol required tests and procedures are completed as described.

8.2.1. Cognition Tests and Quality of Life Assessments

Patients will perform a battery of cognition and quality of life tests, including the CDR-SB, CDR, MMSE, NPI, and EQ-5D-5L throughout the study to assess cognition. Tests, with the exception of the CDR battery, will be performed by paper only. The CDR battery will be performed using an electronic device.

8.2.1.1. Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB)

Clinical Dementia Rating Scale is a global assessment instrument that yields global score and a sum of boxes score. The Clinical Dementia Rating Scale is derived from a semi-structured interview with the participant and an appropriate informant, and it rates impairment in 6 categories (memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 = mild, moderate, and severe impairment, respectively. From the 6 individual category ratings, or box scores, the Clinical Dementia Rating Scale – Global Score is established by clinical scoring rules, for which the Clinical Dementia Rating of 0 = no dementia and Clinical Dementia Rating of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris, 1993). The CDR-SB score is a detailed quantitative general index that provides more information than the Clinical Dementia Rating Scale – Global Score in participants with early (prodromal to mild) dementia (Cedarbaum et al, 2013; Coley et al, 2011). In particular, the CDR-SB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al, 2013).

8.2.1.2. Cognitive Drug Research System (CDR)

The CDR is an automated battery amenable to measurement of cognitive deficits in patients with AD. It consists of performance tasks measuring attention, working memory, episodic memory, and executive function. It contains 11 tests and is performed on a tablet-like device. The average duration of the battery is approximately 25 minutes.

The CDR is performed at the time points listed in the SoA (Table 1). Two training sessions will be conducted at least 30 minutes apart during the screening period to allow patients to become familiar with the procedure, reduce test anxiety, reduce learning effects, and produce a stable baseline assessment.

8.2.1.3. Mini-Mental State Examination Scale (MMSE)

The MMSE is a brief 30-point questionnaire used to assess cognitive impairment with lower scores indicating greater impairment. The MMSE assesses 11 categories of cognition including orientation to time, memory, attention, concentration, naming, repetition, comprehension, and the ability to create a sentence and to copy 2 intersecting polygons. The total scores on the scale ranges from 0 to 30 with lower scores indicating greater impairment.

The MMSE will be administered at the time points indicated in the SoA (Table 1). The MMSE will be administered by a trained member of the investigational team. At each site, the same individual, whenever possible, will perform the MMSE evaluation on a specific patient throughout the study. The screening MMSE will be used for purposes of determining patient eligibility and does not need to be reconciled with the baseline MMSE score.

8.2.1.4. Neuropsychiatry Inventory (NPI)

The NPI is a rater-administered, fully structured interview in which all questions are provided and read verbatim. The sole source of information is the interview with a caregiver who knows the patient well. This study uses the NPI version with 10 behavioral domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior. The NPI total score is calculated by adding the scores of the domains (each domain scores range from 0 to 12). The NPI total score ranges from 0 to 120 with higher scores indicating greater behavioral impairment.

The NPI-D scores in each of the domains are not included in the NPI total score. The NPI-D total score is calculated by adding the scores of caregiver distress in each of the domains (score ranges from 0 to 5 in each domain). The NPI-D total score ranges from 0 to 50 with higher scores indicating greater distress.

The NPI will be administered at the timepoints indicated in the SoA (Table 1). The NPI will be administered by an independent, trained, and certified member of the investigational team. At

each site, the same individual, whenever possible, will perform the NPI evaluation on a specific patient throughout the study.

8.2.1.5. EuroQol 5-Dimension 5-Level Health Related Quality of Life Scale (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from “no problem” to “severe problem”. Two different administrations of the EQ-5D-5L will be performed at baseline and timepoints indicated in the SoA (Table 1). First, the participant’s caregiver will provide a proxy-rating of the patient’s health status. Second, the caregiver will provide a self-report of his or her own health status. In both situations, the EQ-5D-5L questionnaire will be completed by the participant’s caregiver.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.3.1. Physical Examinations

- Physical examination as part of EoS procedures in lead-in Protocol TB006AD2102 will be used as baseline assessment for this study if they are done within 28 days.
- A complete physical examination at the baseline and EoS visit for this OLE study will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- The neurological examination will assess mental status, motor and sensory skills, hearing and speech, vision, coordination, and balance.
- Height and weight will also be measured and recorded. Height will only be measured at screening.
- A brief physical examination at visits other than baseline and EoS visit will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Oral temperature, heart rate, respiratory rate, blood pressure, and orthostatic blood pressure will be assessed as indicated in the SoA (Table 1).
- Blood pressure and pulse measurements will be assessed with a patient in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be taken before blood collection for laboratory tests, if that is scheduled for the same time point.

8.3.3. Electrocardiograms

- ECGs (12-lead) will be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Single measurements are acceptable at all-time points. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- On non-dosing days, effort should be made to perform 12-lead ECGs time-matched with the predose timepoint on dosing days.
- The PI or designated site physician will review and assess all ECGs as Normal, Abnormal, or Not Evaluable. Once signed, the original ECG tracing will be retained with the patient's source documents. At the request of the sponsor, a copy of the original ECG will be made available to the sponsor.

8.3.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed by the central laboratory and the SoA (Table 1) for the timing and frequency.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Table 1).
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- The investigator must review the laboratory report and document this review. The investigator should consider documenting any clinically relevant changes as AEs in the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated at appropriate intervals until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

Not applicable.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

The C-SSRS will be administered as outlined in the SoA (Table 1).

The C-SSRS is a prospective semi structured interview comprised of the following areas of assessment: Ideation, Intensity of Ideation, Behavior, and Lethality. It has been used extensively in global clinical studies (academic and industry sponsored) and in a range of therapeutic areas, disorders and indications, including psychiatry, neurology, obesity, urology, and endocrinology and is FDA approved. It has been used to determine eligibility to enroll at screening and at every follow-up visit to prospectively monitor suicidality during the study. The C-SSRS was developed for use in clinical studies and can be administered by nonmental health professionals with training. All C-SSRS raters for this study will have a certificate that verifies training completion and allows them to rate in this study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's LAR).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the time of the first study drug administration until Week 113 at the timepoints specified in the SoA (Table 1). Any AE that begins in a lead-in study and is ongoing at the time of the first dose of study drug in the OLE will be included as an AE in the OLE. This includes events occurring during the initial visit in the study, regardless of whether or not the study drug has been administered. All AEs reported after the initiation of study drug will be considered treatment-emergent AEs.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in patients with AD and can be serious/life threatening:

- Anxiety and psychosis

- Dysphagia and other eating disorders
- Exacerbation of AD
- Injuries from falls

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded in the patient's CRF when reported. These DREs will be reviewed by the Medical/Scientific Monitor on a routine basis (see Section 10.1.5).

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4.6. Adverse Events of Special Interest

Not applicable.

8.5. Pharmacokinetics

8.5.1. Pharmacokinetics

- Whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of TB006 as specified in the SoA (Table 1).
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of TB006. Each plasma will be divided into 2 aliquots (1 each for PK and a backup). Samples collected for analyses of TB006 (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6. Pharmacodynamics

8.6.1. Cognition Test

For cognition testing, see Efficacy Assessments (see Section 8.2.1).

[redacted]

8.7. Genetics

Not applicable.

8.8. Immunogenicity Assessments

Antibodies to TB006 will be evaluated in plasma samples collected from all patients according to the SoA (Table 1). Additionally, plasma samples should also be collected at the final visit from patients who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Anti-TB006 antibodies will be determined on plasma samples collected for plasma PK determinations, and no additional blood samples need to be obtained.

Plasma samples will be screened for antibodies binding to TB006 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to TB006 and/or further characterize the immunogenicity of TB006.

The detection and characterization of antibodies to TB006 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for TB006 plasma concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug(s).

8.9. Total Volume of Blood Sampling

Table 4 presents the number of blood samples and the total volume of blood that will be collected throughout the study.

Table 4. Summary of Blood Sample Volumes

	Approximate Sample Volume per Collection (mL)	No. of Collection Timepoints	Approximate Total Volume Collected (mL)
Clinical laboratory tests	11	6	66
PK and ADA sampling	6	5	30
PK only	4	7	28
PD Blood sampling	6	7	42
		Total blood volume estimate	166

ADA = anti-drug antibody; PD = pharmacodynamic(s); PK = pharmacokinetic(s)

9. Statistical Considerations

9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested in this study, since the primary objective is to assess the safety, tolerability, and PK of TB006.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Patient Analysis Set	Description
Screened Population	All patients who have completed the lead-in study.
Enrolled Population	All screened patients who agree to participate in this study or met reconfirmed eligibility (if the patient discontinued from lead-in study > 28 days before screening for this study) and provided signed informed consent (or assent).
Safety analysis set (SAS)	All patients who take at least 1 dose of study drug under this protocol. Patients will be analyzed according to the study drug they received
Safety analysis set-Adverse event (SAS-AE)	All patients who take at least 1 dose of study drug under this protocol or lead-in study TB006AD2102. Patients will be analyzed according to the study drug they receive.
Pharmacokinetic set (PKS)	All patients who received their assigned dose of TB006 and have at least 1 post-dose blood sample with measurable TB006 concentrations.
Pharmacodynamic set (PDS)	All patients who received at least 1 dose of study drug and have at least 1 postdose evaluable PD/efficacy assessment.

The Enrolled Population is used to analyze disposition and protocol deviations. The SAS-AE will be used for all AE related displays and SAS will be used for all other safety analyses. The pharmacokinetic analysis set (PKS) will be used for all PK analyses. Efficacy and PD analysis will be performed using the PDS.

If there is any case of an enrolled patient not treated, then demographic tables will be repeated by Enrolled Population.

9.3. Statistical Analyses

9.3.1. General Considerations

No formal statistical hypothesis testing will be performed in this study. All demographic, safety, PK and PD data will be listed and summarized in tabular format by descriptive (n, mean, SD, median, Q1 and Q3, minimum and maximum) and/or summary (n [%]) statistics as appropriate. PK data will also be displayed graphically as appropriate.

Continuous variables will be summarized using descriptive statistics. Categorical/discrete variables will be summarized using summary statistics showing the number and percentage of patients within a particular category.

9.3.2. Primary Endpoints Analysis

9.3.2.1. Safety and Tolerability

Primary safety and tolerability endpoints include:

- Incidence of AEs and SAEs throughout the study
- Summary of ECGs throughout the study
- Summary of clinical laboratory assessments throughout the study
- Summary of vital signs assessments throughout the study
- Summary of physical and neurological examinations throughout the study

All AEs will be coded using the most recent version of the MedDRA. The incidence of AEs will be summarized by SOC and PT. Similar summaries will be produced for AEs by severity, SAEs, treatment related AEs, and AEs leading to discontinuation. AEs are collected from the first dose of study drug; thus, all AEs are considered treatment emergent AEs.

The ECG results will be presented by visit, including the QT, QTc, QRS, RR, PR intervals, as well as change from baseline values, and clinically significant changes in heart rate and rhythm.

Reported values and change from baseline values of hematology, clinical chemistry, and urinalysis (and the determinations relevant to the normal ranges and appropriate clinically significant or CTCAE toxicity gradings), will be summarized by laboratory test for each assessment day, using appropriate descriptive/summary statistics.

Vital signs (systolic and diastolic blood pressure, orthostatic blood pressure, pulse rate, respiratory rate, and oral temperature) will be summarized by assessment day showing absolute values, change from baseline values, and clinically significant changes (including orthostasis) using appropriate descriptive statistics.

Physical and neurological examinations will be summarized by assessment day showing shift from baseline.

The C-SSRS assessment will be presented in a by-patient listing.

9.3.2.2. Pharmacokinetics

Primary PK endpoints include:

- Summary of plasma concentration of TB006 over time throughout the study

Plasma concentrations over time will be presented, showing both individual and mean concentrations by treatment. For PK analysis, descriptive summary statistics along with geometric mean, GSD, arithmetic CV%, and GCV% for plasma concentration of TB006 over time will be presented.

Further details on the statistical analysis will be provided in the SAP.

9.3.2.3. Immunogenicity

The incidence of ADA status will be summarized by treatment over time.

Further details on the statistical analysis will be provided in the SAP.

9.3.3. Secondary Endpoint(s) Analysis

The Pharmacodynamics/cognitive measures are secondary endpoint for the study and includes following measures:

- Change from Baseline through Week 101 on the CDR-SB score
- Change from Baseline through Week 101 on the CDR battery composite scores and individual task measures
- Change from Baseline through Week 101 on the MMSE score
- Change from Baseline through Week 101 on the NPI score
- Change from Baseline through Week 101 on the EQ-5D-5L total score

[redacted]

Further details on the statistical analysis will be provided in the SAP.

9.3.4. Exploratory Endpoints

[redacted]

9.3.5. Other Analysis

The patient disposition showing numbers screened, enrolled, treated, completed, and discontinued from the study will be summarized. For those patients who discontinued the study prematurely, the reason for discontinuation will be summarized.

All patient data will be reviewed for the occurrence of protocol deviations. Summaries will be presented showing the numbers of patients with deviation term.

Demographic variables to be summarized will include age, gender, race, ethnicity, height, weight, and BMI. Baseline characteristics to be summarized will include medical history.

Prior and concomitant medications will be summarized showing the number and percentage of patients taking each medication. Medications will be coded using the WHO DD preferred name.

Also, the protocol deviation observed throughout the trial will be listed.

9.4. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

9.5. Handling of Missing Data

There will be no imputation of missing data. Only the missing dates for adverse events, medications/procedures will be imputed for identification/calculation purposes. The details of imputation will be outlined in SAP.

9.6. Sample Size Determination

Up to 50 de novo patients identified by the sponsor and meeting the eligibility criteria, and all patients who have completed lead-in Protocol TB006AD2102 (either Part 1 or Part 2) are eligible to participate in this study, where completion of Protocol TB006AD2102 is defined as:

- Following through to the Day 104 visit or
- Early withdrawal for reasons other than adverse events after receiving all 5 doses of TB006 and completing the early termination visit.

All eligible patients from lead-in Protocol TB006AD2102 will be contacted to be enrolled in this study, including those eligible for the lead-in study but were not enrolled (de novo). From these eligible patients, all who provided signed informed consent (or assent) to participate and who have passed the screening criteria, will be considered enrolled patients.

No formal sample size calculations were performed for this study. The estimated number of participants is from the proportion of patients who may complete the lead-in study and the proportion of those who historically enroll in OLE studies. The proposed number of enrolled patients from the lead-in study will be 100 to 120. Additionally, up to 50 de novo patients, identified by the sponsor, may be included. Therefore, a total of approximately 150 to 180 patients will be enrolled.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/ IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the sponsor Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.
- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The source document/ medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF(s) during their participation in the study if the ICF is revised.
- The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.
- A copy of the ICF(s) must be provided to the patient or their legally authorized representative.
- Patients who are rescreened are required to sign a new ICF.
- The investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study unless it is a local requirement. The investigator will then inform the primary care physician. If the patient agrees to such notification, the investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the patient's medical record.
- If a patient is unable to read, or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to patients is read and explained to the patient or the patient's legally acceptable representative, and after the patient or the patient's legally acceptable representative has orally consented to the patient's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent

form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative, and that informed consent was freely given by the patient or the patient's LAR (Refer to Section 4.8.9 of the ICH GCP guideline).

10.1.4. Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator must ensure that the patient's confidentiality is maintained for documents submitted to the sponsor.
- For SAEs reported to the sponsor, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).
- Documents that are not submitted to the sponsor (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.
- In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(ies), and the IRB/IEC direct access to review the patient's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.
- The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study related records, including personal information.

10.1.5. Committees Structure

Not applicable.

10.1.6. Dissemination of Clinical Study Data

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by local laws and regulations.

10.1.7. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or CRFs or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided during site training and linked to the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after the last marketing approval in an ICH region or at least 2 years have elapsed since the formal study discontinuation of clinical development of the study drug (eg, via notification of the Federal Drug Administration [FDA] or local regulatory authority), unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from (sponsor's) Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.
- Retention of study documents will be governed by the Clinical Trial Agreement.
- All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the printed CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in Site Trial Binder or other site communication.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Protocol Deviation

There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

The investigator should not deviate from the protocol, except where necessary for patient safety. If other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Medical/Scientific Monitor to determine the appropriate course of action.

The investigator and study staff should adhere to the time points for all procedures to the extent possible. However, circumstances that result in delays are understandable. If delays are significant (ie, > 10 minutes for vital signs) or result in a compromised ability to interpret data (ie, ECG delays that prohibit time-matched comparisons), these will be considered protocol deviations.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the investigator.
- Discontinuation of further study drug development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.11. Publication Policy

- Data from this study are the property of the sponsor, TrueBinding, Inc. Data may not be disclosed by the investigator(s) to any external source without the permission of TrueBinding, Inc.
- If an investigator wishes to present or publish data in the public domain, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.12. Sample Storage and Destruction

- Any blood, PK sample collected according to the SoA (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study

patients. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

- All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.
- If informed consent is provided by the patient, TrueBinding can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the [insert therapeutic area, eg, Inflammatory conditions], the dose response and/or prediction of response to TB006, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 15 years.
- Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the patient's medical record and are not to be made available to the patient, members of the family, the personal physician, or other third parties, except as specified in the informed consent.
- The patient retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the patient, the investigator is to provide the sponsor with the required study and patient number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by TrueBinding.
- The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5. Protocol-required Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**
hematocrit hemoglobin platelet count RBC count RBC indices: MCH MCV % reticulocytes WBC count with differential: neutrophils lymphocytes monocytes eosinophils basophils	albumin alkaline phosphatase ALT/SGPT AST/SGOT BUN calcium creatinine creatine phosphokinase glucose (non-fasted) HbA1c HDL LDL potassium sodium triglycerides TSH total and direct bilirubin total protein Total cholesterol	specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick microscopic examination (if blood or protein is abnormal)
Study-specific	**Other Screening Tests**	
ADA PK	● Alcohol breathalyzer and drug screen, including but not limited to, opiates, methadone, buprenorphine, methamphetamine, cocaine, and amphetamines) ● Serology, COVID-19 nasal swab test	

ADA = antidrug antibody; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; COVID-19 = corona virus disease 2019; HbA1c = glycosylated Hb; HDL = high density lipoprotein; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PK = pharmacokinetics; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Events

Adverse Event (AE) Definition

- An AE is any untoward medical occurrence in a clinical study/patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Unsolicited and Solicited AE Definition

- An unsolicited AE is an AE that was not solicited using a patient diary and that is communicated by a patient/patient's parent(s)/legally authorized representative (LAR) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The patients/patient's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of patient/patient's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the patient's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the patient/patient's parent(s)/LAR(s) will be collected during an interview with the patients/patient's parent(s)/LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the patient is specifically questioned, and which are noted by the patient in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the patient's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events not Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Severe Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the patient's medical records in lieu of completion of the AE/CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- The investigator must assign the following AE attributes:
    - AE diagnosis or syndrome(s), if known (if not known, signs or symptoms)
    - Dates of onset and resolution (if resolved);
    - Severity (toxicity defined below);

  - Assessment of relatedness to study drug or other protocol-required therapies and
  - Action taken. If AE severity changes, record each change as a single event.
- The following should be considered when recording SAEs:
  - Death is an outcome of an event. The event that results in the death should be recorded and reported on both an SAE and CRF.
  - For hospitalizations, surgical, or diagnostic procedures the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself.

Assessment of Severity

The investigator will make an assessment of intensity for each AE and SAE reported during the study per the NCI CTCAE Version 5.0. Toxicities that are not specified NCI CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (eg, bathing dressing and undressing, feeding self, using the toilet, taking medications).

An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the severity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgement to determine relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data**.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- Causality assessments are defined as below:
    - Causality assessments that indicate the event is "Not Drug Related:
        - Unrelated: The event is related to an etiology other than the study drug administration (the alternative etiology must be documented in the patient's medical record).
        - Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.
    - Causality assessments that indicate the event is "Drug Related:
        - Possible: There is an association between the event and the administration of study drug and there is a plausible mechanism for the event to be related to the study drug; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
        - Probable: There is an association between the event and the administration of study drug and there is a plausible mechanism for the event to be related to the study drug, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: there is an association between the event and the administration of study drug and there is a plausible mechanism for the event to be related to the study drug and causes other than the study drug has been ruled out and/or the event re-appeared on re-exposure to the study drug.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by to

elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the Drug Safety team with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see Section 10.3.5) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see Section 10.3.5) or to the Medical/Scientific Monitor by telephone.
- Contacts for SAE reporting are noted below.

10.3.5. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0

The NCI CTCAE is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only, intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Published date of Version 5.0: 27 Nov 2017, available here:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_R eference_5x7.pdf

from:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with permanent infertility due to 1 of the following:
  a. Documented hysterectomy
  b. Documented bilateral salpingectomy
  c. Documented bilateral oophorectomy
  d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     i. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

  Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Not applicable as female patients should be of non-childbearing potential.

10.5. Appendix 5: National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) - Criteria for Diagnosis of Probable Alzheimer's Disease)

- Criteria for Diagnosis of Probable Alzheimer's Disease
  - Dementia established by clinical examination and documented by a standard test of cognitive function (eg, MMSE, Blessed Dementia Scale, etc.) and confirmed by neuropsychological tests;
  - Significant deficiencies in 2 or more areas of cognition, for example, word comprehension and task-completion ability;
  - Progressive deterioration of memory and other cognitive functions;
  - No loss of consciousness;
  - Onset from age 40 to 90, typically after age 65;
  - No other diseases or disorders that could account for the loss of memory and cognition.
- Diagnosis of Probably Alzheimer's Disease is Supported by:
  - Progressive deterioration of specific cognitive functions: language (aphasia), motor skills (apraxia), and perception (agnosia);
  - Impaired activities of daily living and altered patterns of behavior;
  - A family history of similar problems, particularly if confirmed by neurological testing;
  - The following laboratory results:
    - CSF (lumbar puncture test);
    - Normal electroencephalogram test of brain activity;
    - Evidence of cerebral atrophy in a series of CT scans.
- Other Features Consistent with Alzheimer's Disease:
  - Plateaus in the course of illness progression;
  - CT findings normal for the person's age;
  - Associated symptoms including depression, insomnia, incontinence, delusions, hallucinations, weight loss, sex problems, and significant verbal, emotional, and physical outbursts;
  - Other neurological abnormalities, especially in advanced disease, including increased muscle tone and a shuffling gait.
- Features that Decrease the Likelihood of Alzheimer's Disease:
  - Sudden onset;
  - Such early symptoms as seizures, gait problems, and loss of vision and coordination.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention (if applicable)

Phase 1 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology (Table 6).

Table 6. Phase 1 Liver Chemistry Stopping Criteria and Follow-Up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>Alanine aminotransferase (ALT)-absolute</td><td colspan="2">ALT ≥ 3 x upper limit of normal (ULN)
If ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or international normalized ratio (INR) > 1.5, report as a serious adverse event (SAE).[a, b]
See additional actions and follow-up assessments listed below</td></tr>
<tr><td colspan="3">Required Actions, Monitoring, and Follow up Assessments</td></tr>
<tr><td colspan="2">Actions</td><td>Follow Up Assessments</td></tr>
<tr><td colspan="2">● Immediately discontinue study drug.
● Report the event to the sponsor within 24 hours.
● Complete the liver event CRF and complete an SAE data collection tool if the event also met the criteria for an SAE.[b]
● Perform liver function follow-up assessments.
● Monitor the patient until liver function test abnormalities resolve, stabilize, or return to baseline (see MONITORING).

MONITORING:
If ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN or INR > 1.5:
● Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin, and INR) and perform liver function follow-up assessments within 24 hours.
● Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline.
● A specialist or hepatology consultation is recommended.</td><td>● Viral hepatitis serology.[c]
● Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend.
● Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH).
● Fractionate bilirubin, if total bilirubin 2 x ULN
● Obtain complete blood count with differential to assess eosinophilia
● Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) CRF.
● Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) on concomitant medications CRF.
● Record alcohol use on the liver event alcohol intake CRF.</td></tr>
</table>

If ALT ≥ 3 x ULN AND bilirubin < 2 x ULN and INR ≤ 1.5: ● Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin, and INR) and perform liver function follow-up assessments within 24 to 72 hours. ● Monitor patients weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	**If ALT ≥ 3 x ULN AND** total bilirubin ≥ **2 x ULN or INR > 1.5** obtain the following in addition to the assessments listed above: ● Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. ● Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week [James et al, 2009]). ● Liver imaging (ultrasound, magnetic resonance, or CT scan) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is not immediately available, discontinue study drug if ALT ≥ 3 × ULN **and** bilirubin ≥ 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick,** which is indicative of direct bilirubin elevations, suggesting liver injury.
b. All events of ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT ≥ 3 x ULN **and** INR > 1.5, may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to patients receiving anticoagulants.

Includes: hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.A patient who met liver chemistry stopping criteria cannot restart the study drug unless all of the following conditions are met:

- TrueBinding, Inc. approval **is granted** (as described below).
- IRB/IEC approval is obtained.
- Separate ICF for study drug restart/rechallenge is signed by the patient.

If TrueBinding, Inc. approval to restart/rechallenge the patient with the study drug **is not granted**, then the patient must permanently discontinue the study drug and may continue in the study for protocol-specified follow-up assessments.

10.6.1. Rechallenge Following Liver Chemistry Events that are Possibly Related to Study Drug

- Following study drug-induced liver injury, rechallenge is associated with 13% mortality across all study drugs in prospective studies (Andrade et al, 2009). Clinical outcomes vary with nearly 50% fatality with halothane readministered within 1 month of the initial injury. However, some interventions seldom result in recurrent liver injury or fatality.
- Risk factors for a fatal rechallenge outcome include:
    - Hypersensitivity with initial liver injury (eg, fever, rash, eosinophilia) (Andrade et al, 2009).
    - Jaundice or bilirubin > 2 x ULN with initial liver injury (direct bilirubin > 35% of total).
    - Ongoing severe liver injury defined by ALT $\geq$ 3 x ULN AND bilirubin $\geq$ 2 x ULN (direct bilirubin >35% of total) OR INR $\geq$ 1.5.
    - SAE or fatality previously observed with rechallenges (Hunt, 2010; Papay et al, 2009).
    - Evidence of drug-related preclinical liability (eg, reactive metabolites, mitochondrial impairment) (Hunt, 2010).
- Rechallenge refers to resuming the study drug following drug-induced liver injury (DILI). Because of the risks associated with rechallenge after DILI, this should only be considered if there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit/risk assessment of rechallenge is considered to be favorable.
- Approval by the sponsor for rechallenge with the study drug can be considered when:
    - The Principal Investigator (PI) requests consideration of rechallenge with the study drug for a patient who is receiving compelling benefit with the study drug, that exceeds risk, and for whom no effective alternative therapy is available.
    - IRB/IEC approval for rechallenge with the study drug has been obtained.

If the rechallenge is approved by the sponsor in writing:

- The patient must be provided with a clear description of the possible benefits and risks of the study drug administration including the possibility of recurrent, more severe liver injury or death.
- The patient must provide signed informed consent specifically for the rechallenge with the study drug. Documentation of informed consent must be recorded in the study file.
- The study drug must be administered at the dose specified by the sponsor.

- Patient s approved by the sponsor for rechallenge with the study drug must return to the clinic twice a week for liver chemistry tests until stable liver chemistry tests have been demonstrated, and then standard laboratory monitoring may resume as per protocol.
- If the patient meets protocol-defined liver chemistry stopping criteria after the study drug rechallenge, the study drug should be permanently discontinued.
- The sponsor and the IRB/IEC must be informed of the outcome for the patient following the study drug rechallenge.
- The sponsor must be notified of any adverse events (AEs).

AND/OR

10.6.2. Restart Following Transient Resolving Liver Chemistry Events Not Related to Study Intervention

- Restart refers to resuming the study drug following liver chemistry events for which there are clear underlying causes (other than DILI) (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity.
- Approval by the sponsor for the study drug restart can be considered when:
    - The investigator requests consideration for the study drug restart if liver chemistry events have a clear underlying cause (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis) and liver chemistry tests have improved to normal or are within 1.5 × baseline and ALT < 3 × ULN.
    - Possible DILI has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where the study drug has an identified genetic marker associated with liver injury (eg, lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study drug-related liver injury cannot be excluded, the guidance on rechallenge in the previous part of this appendix will apply.
    - There is no evidence of alcoholic-related hepatitis.
    - IRB/IEC approval of study intervention restart has been obtained.

If restart of study intervention is approved by the sponsor in writing:

- The patient must be provided with a clear description of the possible benefits and risks of study drug administration including the possibility of recurrent, more severe liver injury, liver transplantation, or death.
- The patient must provide signed informed consent specifically for the restart of the study drug. Documentation of informed consent must be recorded in the study file.
- The study drug must be administered at the dose specified by the sponsor.

- Patients approved by the sponsor for restart of the study drug must return to the clinic twice a week for liver chemistry tests until stable liver chemistry tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the patient meets protocol-defined liver chemistry stopping criteria after study drug restart, the study drug should be permanently discontinued.
- The sponsor and the IRB/IEC must be informed of the outcome for the patient following study drug restart.
- The sponsor must be notified of any adverse events.

10.7. Appendix 7: Other Study-specific Appendices or Library Appendices

10.7.1. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Criteria for Major Neurocognitive Disorder (previously Dementia)

Evidence of significant cognitive decline from a previous level of performance in 1 or more of the following domains:

- Learning and memory.
- Language.
- Executive function.
- Perceptual motor.
- Social cognition.
- The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
    - The deficits do not occur exclusively during the course of a delirium.
    - The disturbance is not better accounted for by another Axis I disorder (eg, Major Depressive Disorder, Schizophrenia).

10.8. Appendix 8: Country-specific Requirements (if applicable)

Not applicable.

10.9. Appendix 9: Protocol Amendment History

The following table shows the Summary of Changes for the current amendment.

Amendment 2: 16 Feb 2023

Overall Rationale for Amendment 2

[redacted]

Section Number and Name	Description of Change	Brief Rationale
Global	Updated date, version, amendment number, and minor formatting changes.	Administrative update.
[redacted]	[redacted]	[redacted]
1.3. Schedule of Activities (SoA), Table 1, Footnote a	Removed language related to lumbar puncture	This was an unintended carryover from the lead-in study and was not meant to be included. There are no lumbar punctures in this study.
4.1. Overall Design	[redacted]	[redacted]
5.2. Exclusion Criteria	Removed criteria #10 to #14 related to lumbar puncture.	This was an unintended carryover from the lead-in study and was not meant to be included. There are no lumbar punctures in this study.

Section Number and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]

Amendment 1: 26 Jul 2022

Overall Rationale for the Amendment

As AD is a progressive disease, the proposed patient completion rate of this 2-year study is estimated to be below 30%, and additional long-term exposure data may be required prior to moving forward to Phase 3. Adding de novo patients to the study design is expected to provide additional long-term safety data, providing a better baseline of data needs for future intervals.

Section Number and Name	Description of Change	Brief Rationale
Global	Updated date, version, amendment number, and minor formatting changes.	Administrative update.
Global	Updated any instances of "subjects" with "patients".	Administrative update.
Global Protocol Title	Updated title to include addition of de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
List of Abbreviations	Added "De novo" abbreviation and definition.	De novo patients were added to the study design to increase sample size for long-term safety data.
Section 1.1. Synopsis, Rationale	Paragraph 3 updated to be consistent with Section 2.1 Study Rationale, Paragraph 3.	Administrative update.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis, Overall Design	Paragraph 1 and 2 - Updated to include the addition of de novo patients and eligibility requirements of de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
Section 1.1. Synopsis, Overall Design	Paragraph 3 Sentence 2 – Updated "be observed" to "remain". Paragraph 4 Sentences 1, 2, and 3 – Wording update.	Administrative update.
Section 1.1. Synopsis, Number of Participants	Updated the total number of patients to include additional de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
Section 1.1. Synopsis, Summary of Key Eligibility Criteria	Split eligibility criteria for lead-in study patients and de novo patients into 2 subsections. Added MAD protocol eligibility criteria for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
1.2. Schema	Updated to include the addition of de novo patients prior to enrollment.	De novo patients were added to the study design to increase sample size for long-term safety data.
1.3. Schedule of Activities, Table 1, Efficacy and Pharmacodynamic Assessments: Cognition Testing, [redacted] and Blood Samples	[redacted]	To be consistent with the requirements of the Multiple Ascending Dose (MAD) protocol due to the addition of de novo patients.
[redacted]	[redacted]	[redacted]

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities, Table 1, SCR column heading	SCR Heading: Updated to "(Days -28 or -42 to -1)".	Clarification of a longer screening period for de novo patients.
1.3. Schedule of Activities, Table 1, Laboratory Assessments	Updated to "Urine drug and alcohol breathalyzer screening".	Administrative update.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
1.3. Schedule of Activities, Table 1, Abbreviations	Added abbreviation and definition for "q28day".	Administrative update.
1.3. Schedule of Activities, Table 1, Footnote a	Updated to clarify screening (de novo patients) and rescreening procedures (lead-in protocol patients) and added a 42-day screening period is required for de novo patients.	To add clarity with the addition of de novo patients.
1.3. Schedule of Activities, Table 1, Footnote c	Removed "on dosing days".	Administrative update.
1.3. Schedule of Activities, Table 1, Footnote d	Updated to "Predose, then at any time between…".	Administrative update.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities, Table 1, Footnotes General	Footnotes re-lettered due to the addition of Footnote f.	Administrative update.
2.1. Study Rationale	Paragraph 3, first to last sentence – Updated "amyloid plaque deposits" to "amyloid plaque formation" and last sentence – updated "is expected to provide" to "will provide".	Administrative update for consistency with the MAD protocol.
4.1. Overall Design	Paragraphs 1 and 2 - Updated to include the addition of de novo patients and eligibility requirements of de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
4.1. Overall Design	Paragraph 3 Sentence 2 – Updated "be observed" to "remain". Paragraph 5 Sentences 1, 2, and 3 – Wording update.	Administrative update.
4.1.2. Number of Participants	Updated the total number of patients to include additional de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
4.2. Scientific Rationale for Study Design	Paragraph 2: Updated to include wording for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
5.1. Inclusion Criteria	Split eligibility criteria for lead-in study patients and de novo patients into 2 subsections. Added MAD protocol eligibility criteria for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
5.2. Exclusion Criteria	Split eligibility criteria for lead-in study patients and de novo patients into 2 subsections. Added MAD protocol eligibility criteria for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.

Section Number and Name	Description of Change	Brief Rationale
5.4. Screen Failures	Updated to include wording for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
6. Study Intervention(s) and Concomitant Therapy	Paragraph 3 - Updated second paragraph to include wording for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
6.8. Prior and Concomitant Therapy	Paragraph 4 - Updated to include wording for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
6.8. Prior and Concomitant Therapy	Removed unacceptable medications bulleted list.	Administrative update.
8. Study Assessments and Procedures	Bullet point 5 – Removed sentence 2.	Administrative update.
8.1.1. Screening, Enrollment, and Baseline	Combined Paragraph 1 into Paragraph 2 with clarification of procedures for lead-in patients and de novo patients. Paragraph 2 - Updated to clarify screening (de novo patients) and rescreening procedures (lead-in protocol patients).	De novo patients were added to the study design to increase sample size for long-term safety data.
8.1.1. Screening, Enrollment, and Baseline	Deleted Paragraph 2, Sentence 2 and Paragraph 3.	Administrative update.
8.1.2. Demographics and Medical History	Updated to include criteria for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.
8.1.2. Prior Therapy	Updated to include criteria for de novo patients.	De novo patients were added to the study design to increase sample size for long-term safety data.

Section Number and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
8.3.1. Physical Examinations	Clarified wording.	Addition of de novo patients required the update of this section for clarity.
8.4.5. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs	Paragraph 2 – Updated "monitored" to "reviewed" and "safety review committee" to "Medical/Scientific Monitor".	Administrative update.
9.5. Sample Size Estimation	Deleted section.	Not required for this protocol. Covered in Section 9.6. Sample Size Determination.
9.6. Sample Size Determination	Added de novo patient wording and updated the proposed number of patients enrolled in the study.	De novo patients were added to the study design to increase sample size for long-term safety data.
10.2. Appendix 2: Clinical Laboratory Tests, Table 5, Other Screening Tests	Updated to include alcohol breathalyzer. Removed "urine".	Administrative update.
10.6. Appendix 6. Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention (if applicable) Table 6	Updated all instances of " ^{3} " within the table.	Administrative update.
10.6.1. Rechallenge Following Liver Chemistry Events that are Possibly Related to Study Drug	Updated all instances of " ^{3} within this section.	Administrative update.

Section Number and Name	Description of Change	Brief Rationale
10.7 Appendix 7: Other Study-specific Appendices or Library Appendices	Added Section 10.7.1. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria for Major Neurocognitive Disorder (previously Dementia), including criteria bullet points.	Addition of appendix to support the addition of DSM-5 inclusion criteria in applicable sections.

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 2	16 Feb 2023
Amendment 1	26 Jul 2022
Original Protocol	21 Jun 2022

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